NOVEL OXAZOLIDINONE DERIVATIVES

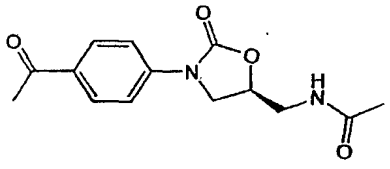
Technical Field

The present invention relates to novel derivatives of oxazolidinone, preparation methods of the same, and pharmaceutical compositions comprising the same for use in an antibiotic.

Background Art

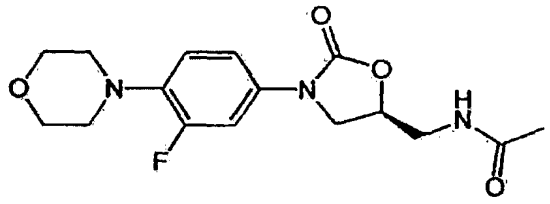
Used as orally administrable antibacterial agents, oxazolidinone compounds are not products of fermentation, but artificially synthesized ones, and various structures of their derivatives are known. For instance, 3-phenyl-2-oxazolidinone derivatives having one or two substituents are stated in U.S. Pat. Nos. 4,948,801, 4,461,773, 4,340,606, 4,476,136, 4,250,318 and 4,128,654. 3-[(Monosubstituted) phenyl]-2-oxazolidinone derivatives of Formula 2 are disclosed in EP 0312000, J. Med. Chem. 32, 1673(1989), J. Med. Chem. 33, 2569 (1990), Tetrahedron, 45, 123(1989)., etc.

<Formula 2>



Pharmacia & Upjohn developed oxazolidinone derivatives of Formulas 3 and 4 (WO 93/23384, WO 95/14684 and WO 95/07271). Having succeeded in gaining the approval of the Food and Drug Administration (FDA) of U.S.A., the oxazolidinone derivative of Formula 3, by the name of 'Zyvox', has came into the market. However, these conventional synthetic oxazolidinone compounds were found to suffer from the disadvantage of showing antibacterial activity against a narrow spectrum of bacteria, being toxic to humans, and being poor in therapeutic activity in vivo. Zyvox may be used restrictively as injection since the solubility of Zyvox against water is inadequate for use in injection, which is about 3mg/ml.

<Formula 3>



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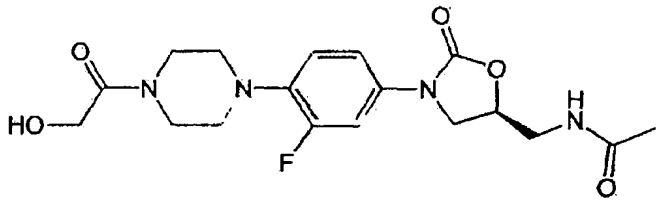


Further, WO 93/09103 discloses derivatives of phenyl oxazolidinone, substituted with heterocyclics such as thiazole, indole, oxazole and quinole, as well as pyridine, at position 4 of the phenyl ring. However, these derivatives of oxazolidinone are known as providing insufficient medicinal effects because the heterocyclics bear simple substituents such as alkyl or amino groups.

In WO 01/94342, synthesizing derivatives of phenyl oxazolidinone, having with pyridine or derivatives of phenyl at position 4 of the phenyl ring was described. The compounds synthesized are potent in inhibitory activity against a broad spectrum of bacteria and are also superior antibiotic to Zyvox. However, the compounds are unable to be formulated as injection because solubility of the same is under 30㎍/㎖.

Accordingly, the intensive and thorough research on oxazolidinone derivatives, conducted by the present inventors aiming to overcome the above problems encountered in prior arts, resulted in the finding oxazolidinone derivatives as well as prodrugs thereof, wherein the prodrugs are prepared by reacting amino acid or phosphate with the oxazolidinone derivatives having hydroxyl group. Further, salts of the oxazolidinone derivatives prodruged were easily synthesized by using amine group of amino acid of the same to synthesize organic acid or inorganic acid and by using a hydroxyl group of phosphate and one selected from sodium and calcium. The oxazolidinone derivatives have excellent effects on antibiotic activity and the solubility of the same is greatly enhanced.

Disclosure of the Invention

Technical problem

It is an object of the present invention to provide novel derivatives of oxazolidinone.

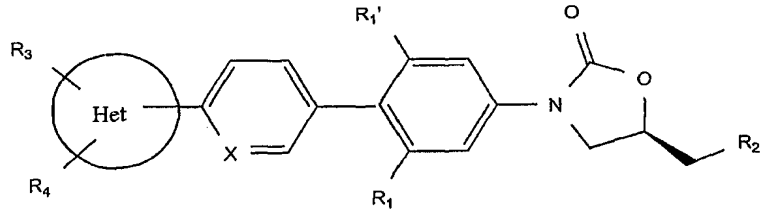
It is another object of the present invention to provide a method of preparing the above-mentioned derivatives.

It is still another object of the present invention to provide a pharmaceutical composition comprising the above-mentioned derivatives for use in an antibiotic.

Technical solution

The present invention provides novel derivatives of oxazolidinone corresponding to Formula 1 defined below.

<Formula. 1>



In the Formula 1, X represents carbon or nitrogen.

R_1 and R_1' respectively represent hydrogen or fluorine.

R_2 represents $-NR_5R_6$, $-OR_7$, triazol, fluorine, alkylphosphate, monophosphate or a metal salt of phosphate;

R_5 and R_6, which are the same or different, respectively represent hydrogen, C. sub. 1-4 alkyl group or acetyl; and

R_7 is hydrogen, C. sub. 1-3 alkyl group or acylated amino acid. When the R_7 is acylated amino acid, amino acid refers to alanine, glycine, proline, isoleucine, leucine, phenylalanine, β-alanine or valine.

Het, which is a heterocyclic ring or a hetero aromatic ring, refers to pyrrole, furan, piperazine, piperidine, imidazole, 1,2,4-triazol, 1,2,3-triazol, tetrazole, pyrazole, pyrrolidine, oxazole, isoxazole, oxadiazole, pyridin, pyrimidine, thiazole or pyrazine.

R_3 and R_4, which are the same or different, respectively refer to hydrogen, C. sub. 1-4 alkyl group that is substituted or unsubstituted with cyano, $-(CH_2)m-OR_7$(m represents 0, 1, 2, 3, 4) or ketone.

The derivatives of oxazolidinone corresponding to Formula 1 may be used for a pharmaceutically acceptable salt, it is preferably an acid addition salt prepared by using pharmaceutically acceptable free acid. The free acid may be inorganic or organic. The inorganic free acid may comprise hydrochloric acid, bromic acid, sulfuric acid, phosphoric acid, etc. The organic free acid may include citric acid, acetic acid, lactic acid, maleic acid, fumaric acid, gluconic acid, methane sulfonic acid, glyconic acid, succinic acid, 4-toluenesulfonic acid, trifluoroacetic acid, galuturonic acid, embonic acid, glutamic acid, aspartic acid, etc.

Preferred compounds of the oxazolidinone derivatives according to the present invention include the following compounds and their structures are described in Table 1.

1) (S)-3-(4-(2-(2-oxo-4-glycyloxymethylpylolidin-1-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide trifluoroacetic acid,

2) (S)-3-(4-(2-(4-glycyloxymethyl-1,2,3-triazol-1-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide trifluoroacetic acid,

3) (S)-3-(4-(2-(5-glycyloxymethylisoxazol-3-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide trifluoroacetic acid,

4) (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-([1,2,4]triazol-1-yl)methyl oxazolidin-2-on,

5) (S)-3-(4-(2-(2-oxo-3-glycyloxypyrolidine-1-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide trifluoroacetic acid,

6) (S)-3-(4-(2-(5-glycyloxymethyl-[1,2,4]oxadiazole-3-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide trifluoroacetic acid,

7) (S)-3-(4-(2-(5-glycyloxymethyl-4,5-dihydroisoxazole-3-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide trifluoroacetic acid,

8) (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-([1,2,3]triazol-2-yl)methyl oxazolidin-2-on,

9) (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-([1,2,3]triazol-1-yl)methyl oxazolidin-2-on,

10) (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-hydroxymethyl oxazolidin-2-on,

11) (S)-3-(4-(4-(4,5-dimethyloxazol-2-yl)phenyl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide,

12) (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on trifluoroacetic acid,

13) (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-([1,2,3]triazol-1-yl)methyl oxazolidin-2-on,

14) (R)-3-(4-(2-([1,2,4]triazol-1-yl)pyridin-5-yl)-3-fluorophenyl)-5-([1,2,3]triazol-1-yl)methyl oxazolidin-2-on,

15) (S)-3-(4-(2-(4,5-dimethyloxazol-2-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl acetamide,

16) (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-hydroxymethyl oxazolidin-2-on,

17) (R)-3-(4-(2-[1,2,4]triazol-1-yl pyridin-5-yl)-3-fluorophenyl)-5-hydroxymethyl oxazolidin-2-on,

18) (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-fluoromethyl oxazolidin-2-on,

19) (S)-3-(4-(2-(imidazole-1-yl)pyridin-5-yl)-3-fluorophenyl)-5-aminomethyl oxazolidin-2-on hydrochloride,

20) (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-valyloxy)methyl oxazolidin-2-on trifluoroacetic acid,

21) (R)-3-(4-(4-(4,5-dimethyloxazol-2-yl)phenyl)-3-fluorophenyl)-5-hydroxymethyl oxazolidin-2-on,

22) (R)-3-(4-(2-([1,2,3]triazol-1-yl)pyridin-5-yl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on trifluoroacetic acid,

23) (R)-3-(4-(4-(4,5-dimethyloxazol-2-yl)phenyl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on trifluoroacetic acid,

24) (R)-3-(4-(2-([1,2,3]triazol-1-yl)pyridin-5-yl)-3-fluorophenyl)-5-hydroxymethyl oxazolidin-2-on,

25) (S)-3-(4-(2-([1,2,3]triazol-2-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide,

26) (S)-3-(4-(4-(4(S)-hydroxymethyl-4,5-dihydroxazole-2-yl)phenyl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide,

27) (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazole-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on trifluoroacetic acid,

28) (S)-3-(4-(4-(4-hydroxymethylthiazol-2-yl)phenyl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide,

29) (R)-3-(4-(2-([1,2,3]triazol-2-yl)pyridin-5-yl)-3-fluorophenyl)-5-hydroxymethyl oxazolidin-2-on,

30) (S)-3-(4-(4-(4-glycyloxymethylthiazol-2-yl)phenyl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide trifluoroacetic acid,

31) (S)-3-(4-(4-(4-cyanomethyl thiazol-2-yl)phenyl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide,

32) (R)-3-(4-(4-(4-cyanomethyl thiazol-2-yl)phenyl)-3-fluorophenyl)-5-hydroxymethyl oxazolidin-2-on,

33) (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-methoxymethyl oxazolidin-2-on,

34) (R)-3-(4-(4-(4-cyanomethyl thiazol-2-yl)phenyl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on trifluoroacetic acid,

35) (R)-3-(4-(2-([1,2,3]triazol-2-yl)pyridin-5-yl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on trifluoroacetic acid,

36) (R)-3-(4-(4-(4-hydroxymethyl thiazol-2-yl)phenyl)-3-fluorophenyl)-5-([1,2,3]triazol-1-yl)methyl oxazolidin-2-on,

37) (R)-3-(4-(4-(4-glycyloxymethyl thiazol-2-yl)phenyl)-3-fluorophenyl)-5-([1,2,3]triazol-1-yl)methyl oxazolidin-2-on trifluoroacetic acid,

38) (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3,5-difluorophenyl)-5-hydroxymethyl oxazolidin-2-on,

39) (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3,5-difluorophenyl)-5-hydroxymethyl oxazolidin-2-on,

40) (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(N,N-dimethylaminomethyl)oxazolidin-2-on,

41) (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(N-methylaminomethyl)oxazolidin-2-on,

42) (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-alanyloxy)methyl oxazolidin-2-on trifluoroacetic acid,

43) (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-valyloxy)methyl oxazolidin-2-on hydrochloride,

44) (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-alanyloxy)methyl oxazolidin-2-on hydrochloride,

45) (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on hydrochloride,

46) (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-prolinyloxy)methyl oxazolidin-2-on trifluoroacetic acid,

47) (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-prolinyloxy)methyl oxazolidin-2-on hydrochloride,

48) (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on hydrochloride,

49) (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(β-alanyloxy)methyl oxazolidin-2-on trifluoroacetic acid,

50) (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(β-alanyloxy)methyl oxazolidin-2-on hydrochloride,

51) (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-alanyloxy)methyl oxazolidin-2-on trifluoroacetic acid,

52) (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-alanyloxy)methyl oxazolidin-2-on hydrochloride,

53) (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-valyloxy)methyl oxazolidin-2-on trifluoroacetic acid,

54) (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-valyloxy)methyl oxazolidin-2-on hydrochloride,

55) (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-prolinyloxy)methyl oxazolidin-2-on trifluoroacetic acid,

56) (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-prolinyloxy)methyl oxazolidin-2-on hydrochloride,

57) (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(β-alanyloxy)methyl oxazolidin-2-on trifluoroacetic acid,

58) (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(β-alanyloxy)methyl oxazolidin-2-on hydrochloride,

59) (R)-[3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl disodiumphosphate,

60) (R)-[3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl disodiumphosphate,

61) (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-hydroxymethyl oxazolidin-2-on,

62) (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on trifluoroacetic acid,

63) (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on hydrochloride,

64) (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-alanyloxy)methyl oxazolidin-2-on trifluoroacetic acid,

65) (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-alanyloxy)methyl oxazolidin-2-on hydrochloride,

66) (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-valyloxy)methyl oxazolidin-2-on trifluoroacetic acid,

67) (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-valyloxy)methyl oxazolidin-2-on hydrochloride,

68) (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(β-alanyloxy)methyl oxazolidin-2-on trifluoroacetic acid,

69) (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(β-alanyloxy)methyl oxazolidin-2-on hydrochloride,

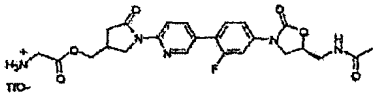
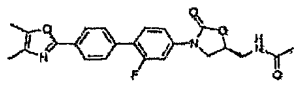
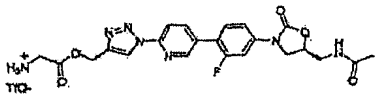
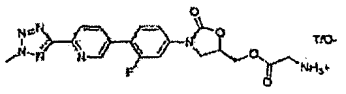
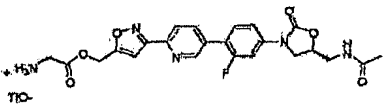
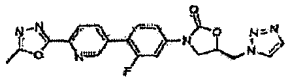
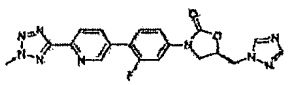
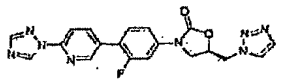
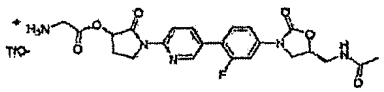
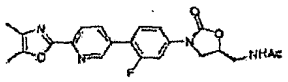
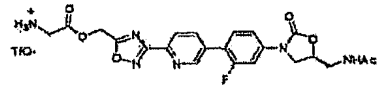
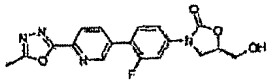
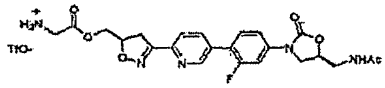
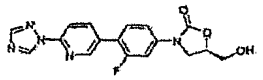
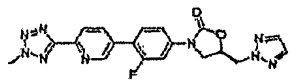
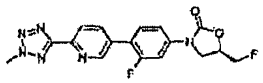
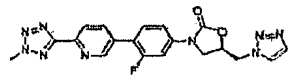
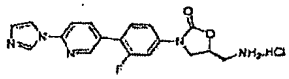
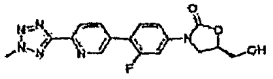
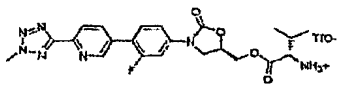
70) (R)-[3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl disodiumphosphate,

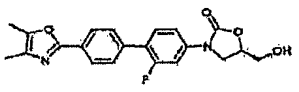
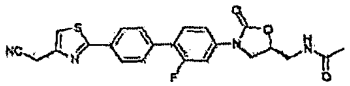
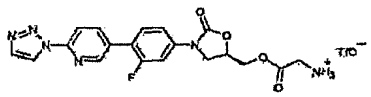
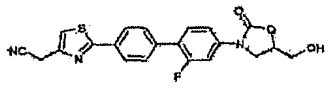
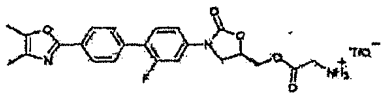
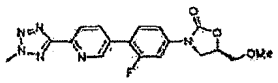
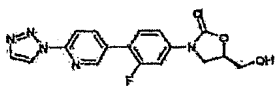
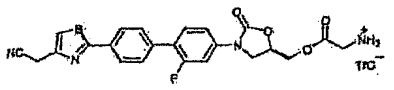
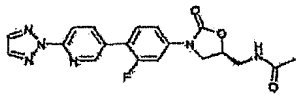
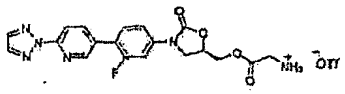
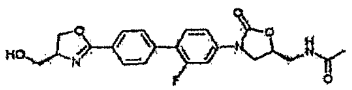
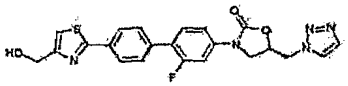
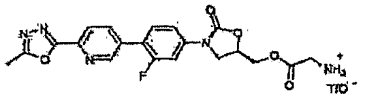
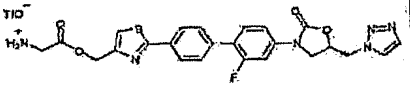
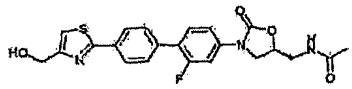
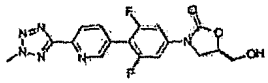
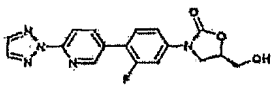
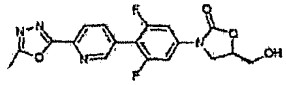
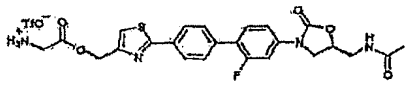
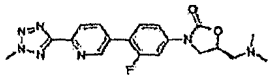
71) (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-([1,2,3]triazol-1-yl)methyl oxazolidin-2-on,

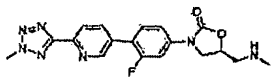
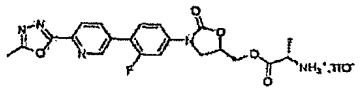
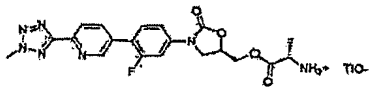
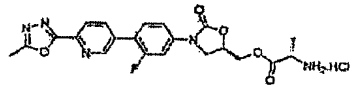
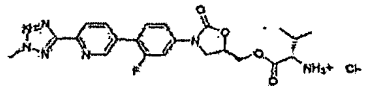
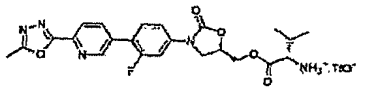
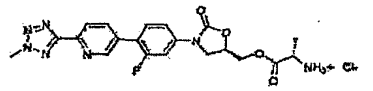
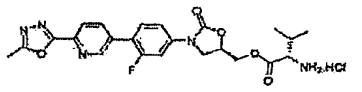
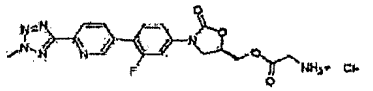
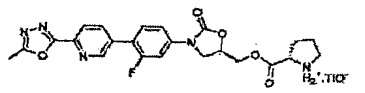
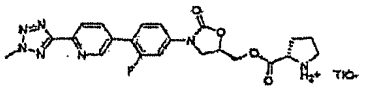
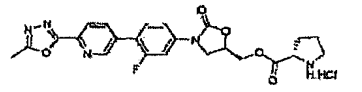
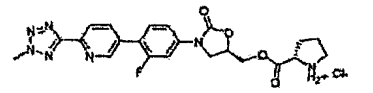
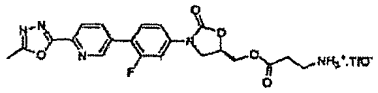
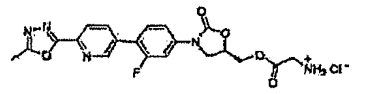
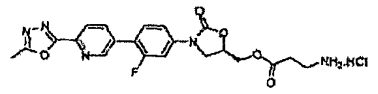
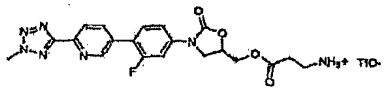
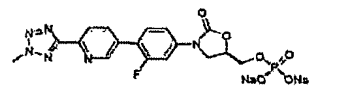
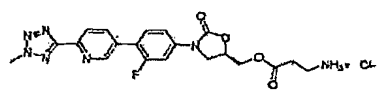
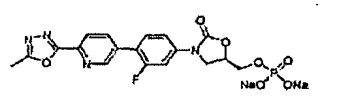
72) mono-[(R)-[3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl] phosphate, and

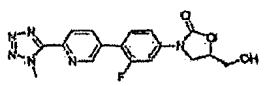
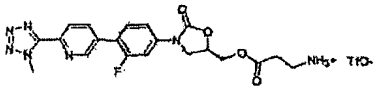
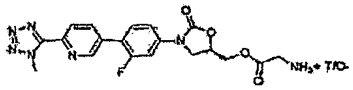
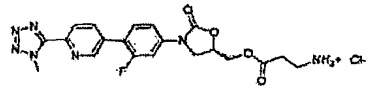
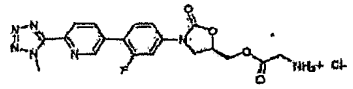
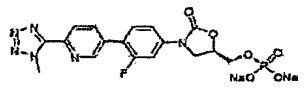
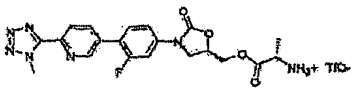
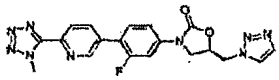
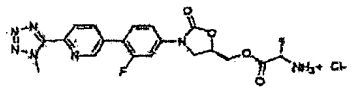
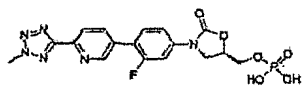
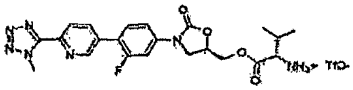
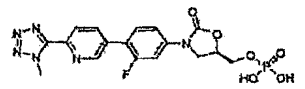
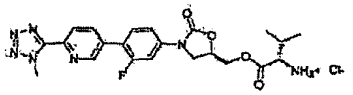
73) mono-[(R)-[3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl] phosphate.

[Table 1]

Compound	Structure	Compound	Structure
1		11	
2		12	
3		13	
4		14	
5		15	
6		16	
7		17	
8		18	
9		19	
10		20	

Compound	Structure	Compound	Structure
21		31	
22		32	
23		33	
24		34	
25		35	
26		36	
27		37	
28		38	
29		39	
30		40	

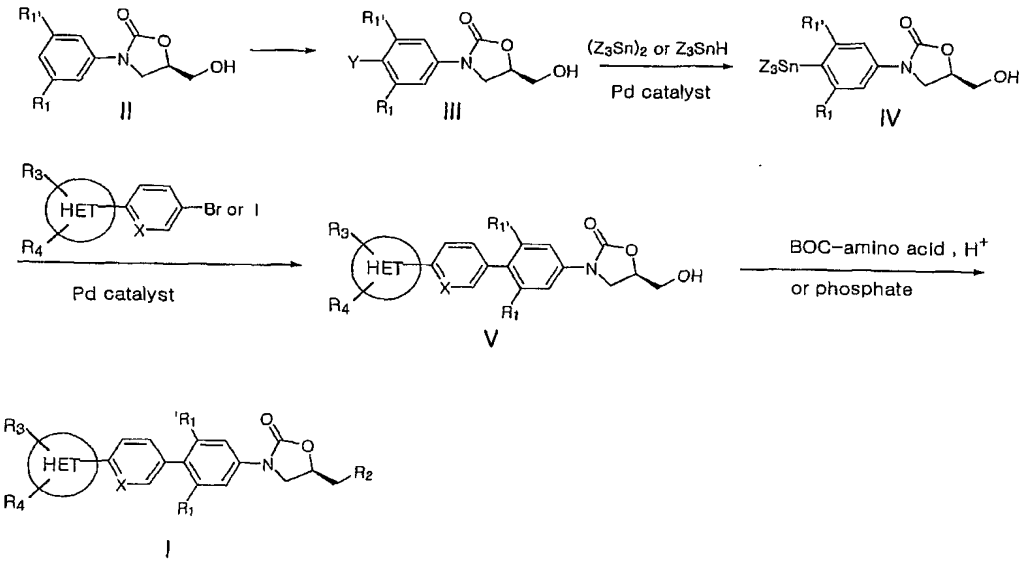
Com-pound	Structure	Com-pound	Structure
41		51	
42		52	
43		53	
44		54	
45		55	
46		56	
47		57	
48		58	
49		59	
50		60	

Compound	Structure	Compound	Structure
61		68	
62		69	
63		70	
64		71	
65		72	
66		73	
67			

In Table 1, 'Ac' represents acetyl and 'TfOH' refers to trifluoroacetic acid.

Further, the present invention provides a method of preparing the derivatives of oxazolidinone corresponding to Formula 1, as shown in Scheme 1 is defined below.

<Scheme 1>



In the Scheme 1, Z represents C. sub. 1~4 alkyl group, X, R_1, R_1', R_2, R_3 and R_4 are as defined in Formula 1 and Y represents halogen.

The method of preparing the derivatives of oxazolidinone according to the present invention comprises;

substituting a halogen atom for a hydrogen atom on phenyl of a derivative(II) of hydroxymethyloxazolidinone thereby to form a derivative(III)(Step 1);

substituting stannyl for a halogen atom(Y) of the derivative(III) to form a derivative(IV)(Step 2);

reacting the derivative(IV) with pyridine or phenyl derivative that is substituted to bromine or iodine to form a derivative(V) of oxazolidinone having pyridine ring or phenyl ring(Step 3); and

reacting the derivative(Ⅴ) with amino acid having a protecting group and then with acid thereby to eliminate the protecting group and to form salts of the compounds corresponding to Formula 1, or subjecting the derivative(Ⅴ) to react with phosphate and then with metallic salt thereby to form salts of the compounds corresponding to Formula 1(Step 4).

In the Step 1, the derivative(Ⅱ) of hydroxymethyloxazolidinone may be synthesized by conventional methods. For example, a method may comprise substituting an amino group of anilin for a benzyloxycarbonyl group and reacting a substituted compound with glycidylbutylate in a state of strong bases thereby to form the derivative(Ⅱ). The state may be prepared by adding a strong base; preferably the strong base may include *n*-butyllitium, *sec*-butyllitium, *tert*-butyllitium, etc., more preferably *n*-butyllitium. Further, it is preferable to subject the method at a temperature of about –78℃ in liquid nitrogen.

The Step 1 is subjected to substitute a hydrogen atom of phenyl group of the derivative(Ⅱ) for a halogen atom, preferably for an iodine atom. When the hydrogen atom is substituted for the iodine atom, the substituted reaction may be subjected preferably by adding iodine monochloride(ICI) or trifluoroacetic acid silver salt(CF_3COOAg) and adding iodine at room temperature.

The Step 2 is subjected the derivative(Ⅲ) to react with hexamethylditin, hexabutylditin or tributyltin hydride by adding a catalyst of palladium to form the derivative(Ⅳ) of which iodine atom is substituted for a trimethylstannyl group or a tributylstannyl group. The catalyst of palladium may comprise

dichlorobistriphenylphosphine palladium(II), tetrakistriphenylphosphine palladium(0), etc. It is preferred to carry out the Step 2 in a solvent of 1,4-dioxan, dimethylformamide, tetrahydrofuran, 1-methyl-2-pyrolidone, etc. at a temperature of about 90 to 150 ℃.

The Step 3 is carried out by reacting the derivative(IV) with a compound having hetero ring on phenyl or pyridine ring thereby to form the derivative(V). A catalyst of palladium added in the Step 3 may be identical to that of palladium in Step 2. It is preferred to carry out the Step 3 in a solvent of dimethylformamide, 1-methyl-2-pyrolidone, etc. at a temperature of about 100 to120 ℃.

The Step 4 is performed by reacting the derivative(V) with amino acid that is protecting an amino group with t-butyloxycarbonyl, dicyclohexylcarbodiimide and 4-dimethylaminopyridine thereby to form the derivative(I) having amino group. The amino acid may include alanine, glycine, proline, isoleucine, leucine, phenylalanine, β-alanine, valine, etc. A solvent comprises dimethylformamide, 1-methyl-2-pyrolidone, etc. Preferably, a reaction by adding the derivative(V) with amino acid is carried out by stirring for about 5 hours above at room temperature.

A mixture of the derivative(V) and amino acid reacts to a strong acid such as trifluoroacetic acid, etc. to eliminate a protecting group. The solvent is removed from the mixture and the mixture is crystallized thereby to provide a salt of the derivative of oxazolidinone corresponding to Formula 1. Preferably, a reaction by adding the derivative(V) with amino acid is carried out by stirring for about 2 hours above at room temperature.

The salt of the derivative of formula 1, prepared by using amino acid at position R_3 or R_4, in a method known similarly to the above method, may be gained. (S)-3-(4-trimethylstannyl-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide as a starting material in the method is known and the method is described in WO0194342.

Further, a phosphate metallic salt of the derivative(I) may be formed by adding sodiummethoxide, sodium hydroxide, etc. to a composition in a solvent such as methanol, ethanol etc., the composition is prepared by dissolving the derivative(V) in trimethylphosphate or triethylphosphate, adding phosphorous oxy chloride and stirring for about 12 hours at room temperature. The phosphate metallic salt may be produced by reacting the derivative(V) with tetrazole and derivates of amidite at room temperature, oxidizing a reacted compound, synthesizing a derivative of alkylphosphate, eliminating alkyl group using a strong acid thereby to form a derivative of phosphate acid, and converting the derivative of phosphate acid into the phosphate metallic salt by the above-mentioned method.

Further, the present invention provides a pharmaceutical composition comprising the derivatives of oxazolidinone corresponding to Formula 1 for use in an antibiotic.

The oxazolidinone derivatives of the present invention show inhibitory activity against a broad spectrum of bacteria, against methicillin resistant Staphylococcus aureus(MRSA) and vancomycin resistant Enterococci(VRE) and

have excellent relatively antibiotic activity with a relatively low concentration thereof or in vivo.

Further, the derivatives of the present invention may exert potent antibacterial activity versus various human and animal pathogens, including Gram-positive bacteria such as Staphylococi, Enterococci and Streptococi, anaerobic microorganisms such as Bacteroides and Clostridia, and acid-resistant microorganisms such as Mycobacterium tuberculosis and Mycobacterium avium.

The derivatives of oxazolidinone, having hydroxyl, are reacted with amino acid or phosphate to form prodrugs thereof. The prodrugs have superior solubility to compounds that are not formed as prodrugs: the solubility of the prodrugs represents above 28㎎/㎖ and the solubility of the compound 10㎎/㎖(compound 10). The prodrugs stabilize in water or acidic solution and change to hydroxylmethyl compounds by being reverted using esterase and phosphatase in a blood thereby to develop easy formulation for injection or oral administration.

The composition of the present invention may comprise at least one effective ingredient having functions similar to those of the derivatives of oxazolidinone.

For formulating a pharmaceutical composition, at least one specie of the compound of formula 1 may be admixed with at least one pharmaceutically acceptable carrier. The pharmaceutical acceptable carrier may include saline solution, sterile water, Ringer's solution, buffered saline solution, dextrose solution, malto-dextrin solution, glycerol, ethanol, etc. According to the user's necessity, the pharmaceutical composition may contain conventional expedient such as

antioxidizing agent, buffer, soil cleaner, etc. Also, the compositions are admixed with diluents, disintegrants, surface active agents, binders, lubricants, aqueous solution, suspension, etc. to be formed for injection, powders, capsules, granules, tablet, etc. Preferably, the formulation is prepared using proper methods described in Remington's Pharmaceutical Science(the newest edition), Mack Publishing Company, Easton PA, etc. according to diseases or ingredients.

The compound of the present invention may be administrated orally or parenterally, such as intravenously, hypodermically, intra-abdominally, topically, etc. The dosage of the compound may vary depending upon the particular compound utilized, the mode of administration, the condition, and severity thereof, of the condition being treated, as well as the various physical factors related to the individual being treated. As used in accordance with invention, satisfactory results may be obtained when the compounds of the present invention are administered to the individual in need at a daily dosage of about 10 mg to about 25 mg per kilogram of body weight, preferably about 13 mg to about 20 mg per kilogram of body weight, more preferably administered each of divided doses to many times per day.

The Lethal Dose (LD_{50}) of the oxazolidinone derivatives shows above 1g/kg in test of acute toxicity so that the derivatives are found stable.

Advantageous Effects

The oxazolidinone derivatives of the present invention show inhibitory activity against a broad spectrum of bacteria and lower toxicity. The prodrugs,

prepared by reacting the compound having hydroxyl with amino acid or phosphate, have high solubility thereof against water.

Further, the derivatives of the present invention may exert potent antibacterial activity versus various human and animal pathogens, including Gram-positive bacteria such as Staphylococci, Enterococci and Streptococi, anaerobic microorganisms such as Bacteroides and Clostridia, and acid-resistant microorganisms such as Mycobacterium tuberculosis and Mycobacterium avium.

Accordingly, the compositions comprising the derivatives of oxazolidinone are used in an antibiotic.

Best Mode For Carrying Out the Invention

The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

Preparation example 1: Preparation of N-Carbobenzyloxy-3-fluoroaniline

3-fluoroaniline 100g was dissolved in 1L of tetrahydrofuran(THF) and the solution was added with 150g(1.8 mol) of sodium bicarbonate($NaHCO_3$). After being cooled to 0℃, the solution was slowly added with 154ml of *N*-carbobenzyloxy chloride(CbzCl) for reaction. While the temperature was maintained at 0℃, the reaction mixture was let to react for 2 hours with stirring. Afterwards, the reaction was extracted with 0.5L of ethyl acetate. The organic layer, after being

separated, was washed with brine, dried over anhydrous magnesium sulfate($MgSO_4$) and concentrated in vacuo. The residue was washed twice with *n*-hexane to afford the title compound as white crystal. 132g. Yield 85%.

Preparation example 2: Preparation of (R)-3-(3-fluorophenyl)-2-oxo-5-oxazolidinylmethanol

132g of N-carbobenzyloxy-3-fluoroaniline 132g prepared in the Preparation example 1 was dissolved in 1.3L of tetrahydrofuran and the solution was cooled to –78℃. 370ml of *n*-buthyllitium(*n*-BuLi, 1.6M /*n*-hexane) was slowly added to the solution in a nitrogen atmosphere, followed by stirring for 10 min. And 84ml of (R)-(-)-glycidylbuthylate was slowly added to the reaction mixture, stirred at the same temperature for 2 hours and allowed to react for 24 hours at room temperature. After completion of the reaction, the solution was added with ammonium chloride (NH_4Cl) solution and extracted with 0.5L of ethyl acetate at room temperature. The organic layer, thus separated, was washed with brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was dissolved in 100ml of ethyl acetate and washed with *n*-hexane to give white crystals, which were purified to the title compound. 80g. Yield 70%.

^{1}H NMR(DMSO-d_6) δ 7.85(t,1H), 7.58(dd,1H), 7.23(dd,1H), 4.69(m,1H), 4.02 (t,1H), 3.80(dd,1H), 3.60(br dd,2H).

Preparation example 3: Preparation of (R)-3-(4-iodo-3-fluorophenyl)-2-oxo-5-

oxazolidinylmethanol

In 300ml of acetonitryl was dissolved 30g of (R)-3-(3-fluorophenyl)-2-oxo-5-oxazolidinylmethanol prepared in the Preparation example 2, and 46g of trifluoroacetic acid silver salt(CF_3COOAg) and 43g of iodide were added to the solution. After being stirred for one day at room temperature, the solution was added with water and was extracted with ethyl acetate. The organic layer, thus separated, was washed with brine and dehydrated. And then the residue was filtered, concentrated in vacuo and dried thereby to form the title compound 44g. Yield 94%.

^{1}H NMR(DMSO-d_6) δ 7.77(t,1H), 7.56(dd,1H), 7.20(dd,1H), 5.20(m,1H), 4.70 (m,1H), 4.07(t,1H), 3.80(m,1H), 3.67(m,2H), 3.56(m,3H)

Preparation example 4: Preparation of (R)-3-(4-tributhylstannyl-3-fluorophenyl)-2-oxo-5-oxazolidinylmethanol

In 660ml of 1,4-dioxan was dissolved 50g of (R)-3-(4-iodo-3-fluorophenyl)-2-oxo-5-oxazolidinylmethanol prepared in the Preparation example 3, 52g of hexabutylditin($(Bu_3Sn)_2$) and 9.3g of dichlorobistriphenylphosphinpalladium were added into the solution, and stirred for 2 hours. The solution was filtered using celite and concentrated in vacuo. The residue was purified by column chromatography and 45g of the title compound was formed.

^{1}H NMR(DMSO-d_6) δ 7.74(m,3H), 5.20(t,1H), 4.71(m,1H), 4.08(t,1H), 3.82(dd,1H), 3.68(m,1H), 3.52(m,1H), 1.48(m, 6H), 1.24(m, 6H), 1.06(m,6H), 0.83(t,9H)

Preparation example 5: Preparation of 2-cyano-5-bromopyridine

In 1L of dimethylformamide was dissolved 100g of 2,5-dibromopyridine, 32g of cupper cyanide and 17.8g of sodium cyanide were added to the solution at room temperature and the solution was stirred at the temperature of 150℃ for 7 hours for reaction. After being cooled to room temperature, the reaction mixture was added with water and extracted with ethyl acetate. The organic layer was washed with brine, dehydrated, filtered and concentrated in vacuo. The title compound 54g was obtained. Yield 70%.

^{1}H NMR($CDCl_3$) δ 8.76(s,1H), 7.98(dd,1H), 7.58(dd,1H)

Preparation example 6: Preparation of 2-(tetrazol-5-yl)-5-bromopyridine

10g of 2-cyano-5-bromopyridine prepared in the Preparation example 5 was dissolved in 100ml of dimethylformamide, 5.33g of sodiumazide, and 4.4g of ammoniumchloride were added to the solution at room temperature, and the solution was stirred at the temperature of 110℃ for 3 hours for reaction. The reaction mixture was added with water and then was extracted with ethyl acetate. The organic layer, thus separated, was washed with brine, dehydrated, filtrated and concentrated in vacuo thereby to obtain 10.5g of the title compound. Yield 85%.

Preparation example 7: Preparation of 2-(1-methyltetrazol-5-yl)-5-bromopyridine and 2-(2-methyltetrazol-5-yl)-5-bromopyridine

10.5g of 2-(tetrazol-5-yl)-5-bromopyridine prepared in the Preparation

example 6 was dissolved in 100ml of dimethylformamide. And then 6.5g of sodiumhydroxide was added to the solution and 9.3g of iodomethane was slowly added to the solution at the temperature of 0℃. The solution was stirred for 6 hours at room temperature, added with water, extracted with ethyl acetate. And then the organic layer was washed with brine, dehydrated, filtrated, concentrated in vacuo and purified by column chromatography to obtain 4g of 2-(1-methyltetrazol-5-yl)-5-bromopyridine and 5g of 2-(2-methyltetrazol-5-yl)-5-bromopyridine.

1) 2-(1-methyltetrazol-5-yl)-5-bromopyridine

^{1}H NMR($CDCl_3$) δ 8.77(t,1H), 8.23(dd,1H), 8.04(dd,1H), 4.46(s,3H)

2) 2-(2-methyltetrazol-5-yl)-5-bromopyridine

^{1}H NMR($CDCl_3$) δ 8.80(t,1H), 8.13(dd,1H), 7.98(dd,1H), 4.42(s,3H)

Preparation example 8: Preparation of 2-(2-methyl-[1,3,4]oxadiazol-5-yl)-5-bromopyridine

In 130ml of acetic anhydride was dissolved 8.6g of 2-(tetrazol-5-yl)-5-bromopyridine prepared in the Preparation example 6. And then the solution was added with 15ml of pyridine and stirred for 3 hours for reaction. The reaction mixture was added with ethyl acetate and extracted to separate organic layer. And then the organic layer was washed with water and brine. The organic layer was dehydrated, filtrated and concentrated in vacuo to give 7.3g of the title compound. Yield 80%.

^{1}H NMR($CDCl_3$) δ 7.99(t,1H), 7.40(dd,1H), 7.27(dd,1H), 1.83(s,3H)

Preparation example 9: Preparation of 2-([1,2,3]triazol-1-yl)-5-bromopyridine and 2-([1,2,3]triazol-2-yl)-5-bromopyridine

20g of 2,5-dibromopyridine was dissolved in 200ml of 1-methyl-2-pyrrolidone. The solution was added with 35g of potasiumcarbonate and stirred for 10 hours at the temperature of 100℃. The reaction mixture was added with ethyl acetate and the organic layer, thus obtained was washed with water and brine. The organic layer was dried, filtered and concentrated in vacuo to provide 6g of 2-([1,2,3]triazol-1-yl)-5-bromopyridine, 4g of 2-([1,2,3]triazol-2-yl)-5-bromopyridine.

1) 2-([1,2,3]triazol-1-yl)-5-bromopyridine

^{1}H NMR($CDCl_3$) δ 8.53(dd,2H), 8.10(d,1H), 8.03(dd,1H), 7.82(s,1H)

2) 2-([1,2,3]triazol-2-yl)-5-bromopyridine

^{1}H NMR($CDCl_3$) δ 8.60(t,1H), 7.97(s,2H), 7.87(s,2H)

Example 1: Preparation of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-hydroxymethyl oxazolidin-2-on (compound 10)

In 150ml of 1-methyl-2-pyrrolidone was dissolved 37g of (R)-3-(4-tributhylstannyl-3-fluorophenyl)-2-oxo-5-oxazolidinylmethanol. The solution was added with 19.7g of 2-(2-methyltetrazol-5-yl)-5-bromopyridine, 10.44g of lithium chloride and 2.9g of dichlorobistriphenylphospine palladium(II) at room temperature and then stirred at the temperature of 120℃ for 4 hours. The reaction mixture was added with water and then extracted with ethyl acetate. The organic

layer, thus separated, was washed with brine, dehydrated, filtrated, concentrated in vacuo and purified by column chromatography to provide 8g of the title compound. Yield 26%.

^{1}H NMR(DMSO-d_6) δ 8.90(s,1H), 8.18(m,2H), 7.70(m,2H), 7.49(dd,1H), 5.25(t,1H), 4.74(m,1H), 4.46(s,3H), 4.14(t,1H), 3.88(dd,1H), 3.68(m,1H), 3.58 (m,1H)

Example 2: Preparation of (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-hydroxymethyl oxazolidin-2-on (compound 16)

The title compound 6.6g(yield 30%) was prepared in a method similar to that of Example 1, except that, 14.3g of 2-(2-methyl-[1,3,4]oxadiazol-5-yl)-5-bromopyridine, instead of 2-(2-methyltetrazol-5-yl)-5-bromopyridine, was used as a starting material.

^{1}H NMR(DMSO-d_6) δ 8.93(s,1H), 8.21(s,2H), 7.71(m,2H), 7.50(dd,1H), 5.25(t,1H), 4.74(m,1H), 4.14(t,1H), 3.89(dd,1H), 3.68(m,1H), 3.59(m,1H), 2.64 (s,3H)

Example 3: Preparation of (R)-3-(4-(2-([1,2,4]triazol-1-yl)pyridin-5-yl)-3-fluorophenyl)-5-hydroxymethyl oxazolidin-2-on (compound 17)

The same procedure as in Example 1 was conducted, except for using, instead of 2-(2-methyltetrazol-5-yl)-5-bromopyridine, 200mg of 2-([1,2,4]triazol-1-yl)-5-bromopyridine as a starting material, to prepare the title compound

150mg(yield 48%).

Example 4: Preparation of (R)-3-(4-(4-(4,5-dimethyloxzol-2-yl)phenyl)-3-fluorophenyl)-5-hydroxymethyl oxazolidin-2-on (compound 21)

The same procedure as in Example 1 was conducted, except for using, instead of 2-(2-methyltetrazol-5-yl)-5-bromopyridine, 1g of 4-(4,5-dimethyloxazol-2-yl)bromobenzene as a starting material, to prepare the title compound 780mg(yield 76%).

^{1}H NMR(DMSO-d_6) δ 7.96(s,1H), 7.94(s,1H), 7.63(m,4H), 7.44(dd,1H), 5.23(t,1H), 4.72(m,1H), 4.12(t,1H), 3.87(dd,1H), 3.68(m,1H), 3.56(m,1H), 2.32 (s,3H), 2.10(s,3H)

Example 5: Preparation of (R)-3-(4-(2-([1,2,3]triazol-1-yl)pyridin-5-yl)-3-fluorophenyl)-5-hydroxymethyloxazolidin-2-on (compound 24)

The same procedure as in Example 1 was conducted, except for using, instead of 2-(2-methyltetrazol-5-yl)-5-bromopyridine, 2g of 2-([1,2,3]triazol-1-yl)-5-bromopyridine as a starting material, to prepare the title compound 1.2g.

^{1}H NMR(DMSO-d_6) δ 8.88(s,1H), 8.76(s,1H), 8.28(d,1H), 8.21(d,1H), 8.01 (s,1H), 7.70(m,2H), 7.51(dd,1H), 5.26(t,1H), 4.75(m,1H), 4.14(t,1H), 3.90 (dd,1H), 3.68(m,1H), 3.58(m,1H)

Example 6: Preparation of (R)-3-(4-(2-([1,2,3]triazol-2-yl)pyridin-5-yl)-3-

fluorophenyl)-5-hydroxymethyl oxazolidin-2-on (compound 29)

The same procedure as in Example 1 was conducted, except for using, instead of 2-(2-methyltetrazol-5-yl)-5-bromopyridine, 1g of 2-([1,2,3]triazol-2-yl)-5-bromopyridine as a starting material, to prepare the title compound 0.7g.

^{1}H NMR(DMSO-d_6) δ 8.74(s,1H), 8.25(dd,1H), 8.23(s,1H), 8.11(d,1H), 7.69(m,3H), 7.49(dd,1H), 5.24(t,1H), 4.75(m,1H), 4.14(t,1H), 3.89(dd,1H), 3.68(m,1H), 3.59(m,1H)

Example 7: Preparation of (R)-3-(4-(4-(4-cyanomethyl thiazol-2-yl)phenyl)-3-fluorophenyl)-5-hydroxymethyl oxazolidin-2-on (compound 32)

The same procedure as in Example 1 was conducted, except for using, instead of 2-(2-methyltetrazol-5-yl)-5-bromopyridine, 1g of 4-(4-cyanomethyl thiazol-2-yl)bromobenzene as a starting material, to prepare the title compound 520mg.

^{1}H NMR(DMSO-d_6) δ 8.04(s,1H), 8.00(s,1H), 7.65(m,5H), 7.47(dd,1H), 5.24(t,1H), 4.74(m,1H), 4.23(s,2H), 4.13(t,1H), 3.88(dd,1H), 3.68(m,1H), 3.59 (m,1H)

Example 8: Preparation of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3,5-difluorophenyl)-5-hydroxymethyl oxazolidin-2-on (compound 38)

The same procedure as in Example 1 was conducted, except for using, instead of (R)-3-(4-tributhylstannyl-3-fluorophenyl)-2-oxo-5-oxazolidinylmethanol, (R)-3-(4-tributhylstannyl-3,4-difluorophenyl)-2-oxo-5-oxazolidinylmethanol as a

starting material, to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.81(s,1H), 8.25(d,1H), 8.10(d,1H), 7.54(d,2H), 5.25 (t,1H), 4.77(m,1H), 4.47(s,3H), 4.13(t,1H), 3.89(dd,1H), 3.68(m,1H), 3.57 (m,1H)

Example 9: Preparation of (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3,4-difluorophenyl)-5-hydroxymethyl oxazolidin-2-on (compound 39)

The same procedure as in Example 1 was conducted by using (R)-3-(4-tributhylstannyl-3, 4-difluorophenyl)-2-oxo-5-oxazolidinylmethanol and 2-(2-methyl-[1,3,4]oxadiazol-5-yl)-5-bromopyridine as a starting material, to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.83(s,1H), 8.25(d,1H), 8.15(d,1H), 7.55(d,2H), 5.25 (t,1H), 4.77(m,1H), 4.13(t,1H), 3.89(dd,1H), 3.68(m,1H), 3.59(m,1H), 2.63 (s,3H)

Example 10: Preparation of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on trifluoroacetic acid (compound 12)

In 25ml of dimethylformamide was dissolved 4g of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-hydroxymethyl oxazolidin-2-on(compound 10). The solution was added 3.34g of 1,3-dicyclohexylcarbodiimide, 2.36g of BOC-glycine and 0.2g of 4-dimethylaminopyridine at room temperature

and then stirred for 10 hours. The reaction mixture was added with water and extracted with ethyl acetate. The organic layer, thus separated, was washed with brine, dehydrated, filtered, concentrated in vacuo and purified by column chromatography. A residue, thus resulted in concentrating in vacuo, was dissolved in 70ml of methylenchloride, added with 30ml of trifluoroacetic acid, and stirred for 2 hours at room temperature. The residue was washed with ethanol and ethyl ether and concentrated in vacuo to obtain the title compound 4.47g. Yield 76%.

^{1}H NMR(DMSO-d_6) δ 8.92(s,1H), 8.19(s,3H), 8.17(m,2H), 7.77(t,1H), 7.69 (dd,1H), 7.49(dd,1H), 5.00(m,1H), 4.46(m,2H), 4.47(s,3H), 4.24(t,1H), 3.92 (dd,1H), 3.90(s,2H)

Example 11: Preparation of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-valyloxy)methyl oxazolidin-2-on trifluoroacetic acid (compound 20)

The title compound was prepared in a method similar to that of Example 10 using BOC-valline, instead of BOC-glycine.

^{1}H NMR(DMSO-d_6) δ 8.92(s,1H), 8.40(s,3H), 8.21(m,2H), 7.76(t,1H), 7.65 (dd,1H), 7.48(dd,1H), 5.05(m,1H), 4.63(dd,1H), 4.47(s,3H), 4.43(dd,1H), 4.28 (t,1H), 4.01(d,1H), 3.93(dd,1H), 2.14(m,1H), 0.98(d,3H), 0.95(d,3H)

Example 12: Preparation of (R)-3-(4-(2-[1,2,3]triazol-1-yl pyridin-5-yl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on trifluoroacetic acid

(compound 22)

The title compound was prepared in a method similar to that of Example 10 using compound 24.

^{1}H NMR(DMSO-d_6) δ 8.87(s,1H), 8.76(s,1H), 8.33(s,3H), 8.29(d,1H), 8.00 (s,1H), 7.77(t,1H), 7.76(t,1H), 7.67(dd,1H), 7.47(dd,1H), 5.02(m,1H), 4.49 (m,2H), 4.23(t,1H), 3.93(m,3H)

Example 13: Preparation of (R)-3-(4-(4-(4,5-dimethyloxazol-2-yl)phenyl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on trifluoroacetic acid (compound 23)

The title compound was prepared in a method similar to that of Example 10 using compound 21.

^{1}H NMR(DMSO-d_6) δ 8.31(s,3H), 7.97(d,2H), 7.64(m,4H), 7.45(dd,1H), 5.01(m,1H), 4.47(m,2H), 4.25(t,1H), 3.94(dd,1H), 3.90(s,2H)

Example 14: Preparation of (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on trifluoroacetic acid (compound 27)

The title compound was prepared in a method similar to that of Example 10 using compound 16.

^{1}H NMR(DMSO-d_6) δ 8.96(s,1H), 8.31(s,3H), 8.22(s,2H), 7.76(t,1H), 7.66 (dd,1H), 7.50(dd,1H), 5.04(m,1H), 4.50(m,2H), 4.25(t,1H), 3.94(dd,1H), 3.91 (s,2H),

2.63(s,3H)

Example 15: Preparation of (R)-3-(4-(4-(4-cyanomethyl thiazol-2-yl)phenyl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on trifluoroacetic acid (compound 34)

The title compound was prepared in a method similar to that of Example 10 using compound 32.

^{1}H NMR(DMSO-d_6) δ 8.25(s,3H), 8.03(d,2H), 7.68(m,5H), 7.44(dd,1H), 5.01(m,1H), 4.48(m,2H), 4.25(m,3H), 3.92(m,3H)

Example 16: Preparation of (R)-3-(4-(2-([1,2,3]triazol-2-yl)pyridin-5-yl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on trifluoroacetic acid (compound 35)

The title compound was prepared in a method similar to that of Example 10 using compound 29.

^{1}H NMR(DMSO-d_6) δ 8.78(s,1H), 8.23(m,2H), 8.22(s,3H), 8.20(s,1H), 8.12 (d,1H), 7.75(t,1H), 7.67(dd,1H), 7.48(dd,1H), 5.01(m,1H), 4.49(m,2H), 4.24 (t,1H), 3.92(dd,1H), 3.89(s,2H)

Example 17: Preparation of (S)-3-(4-(2-(2-oxo-4-glycyloxymethylpyrrolidin-1-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide trifluoroacetic acid (compound 1)

1. The Primary Step

In 14ml of 1-methyl-2-pyrrolidon was dissolved 1.8g of (S)-3-(4-trimethylstannyl-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide. The solution was added 1.03g of 2-(2-oxo-4-hydroxymethylpyrrolidin-1-yl)-5-bromopyridine, 0.55g of lithium chloride and 0.15g of dichlorobistriphenylphosphine palladium(II) at room temperature and then stirred at the temperature of 110℃ for 2 hours. The reaction mixture was added with water and extracted with ethyl acetate. After being washed with brine, the organic layer, thus separated, was dehydrated, filtered, concentrated in vacuo and purified by column chromatography thereby to obtain (S)-3-(4-(2-(2-oxo-4-hydroxymethylpyrrolidin-1-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide 410mg. Yield 21%.

2. The Secondary Step

In dimethylformamide 2.3ml was dissolved 50mg of the compound prepared in the primary step. The solution was added with 35mg of 1,3-dicyclohexylcarbodiamide, 25mg of BOC-glycine and 2.1mg of 4-dimethylaminopyridin at room temperature and then stirred for 10 hours. The reaction mixture was added with water and extracted with ethyl acetate. After being washed with brine, the organic layer, thus separated, was dehydrated, filtrated, concentrated in vacuo and purified by column chromatography. A residue, provided by concentrating, was dissolved in 2ml of methylenchloride, added with 1ml of

trifluoroacetic acid and then stirred for 2 hours at room temperature. The residue was washed with ethanol and ethyl ether, evaporated in vacuo to obtain the title compound 140mg.

^{1}H NMR(DMSO-d_6) δ 8.60(s,1H), 8.40(d,1H), 8.28(s,3H), 8.25(m,1H), 8.08 (dd,1H), 7.63(m,2H), 7.42(dd,1H), 4.76(m,1H), 4.27(s,2H), 4.16(q,2H), 3.87 (s,2H), 3.80(m,2H), 3.42(m,2H), 2.62(m,1H), 2.11(m,1H), 1.83(s,3H)

Example 18: Preparation of (S)-3-(4-(2-(4-glycyloxymethyl-[1,2,3]triazol-1-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide trifluoroacetic acid (compound 2)

The same procedure as in Example 17 was conducted, except for using, instead of 2-(2-oxo-4-hydroxymethylpyrrolidin-1-yl)-5-bromopyridine, 2-(4-hydroxymethyl-[1,2,3]triazol-1-yl)-5-bromopyridine as a starting material, to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.96(s,1H), 8.89(s,1H), 8.22(m,6H), 7.74(t,1H), 7.68 (dd,1H), 7.48(dd,1H), 5.42(s,2H), 4.78(m,1H), 4.19(t,1H), 3.91(s,2H), 3.79 (dd,1H), 3.43(m,2H), 1.83(s,3H)

Example 19: Preparation of (S)-3-(4-(2-(5-glycyloxymethylisoxazol-3-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide trifluoroacetic acid (compound 3)

The same procedure as in Example 17 was conducted, except for using,

instead of 2-(2-oxo-4-hydroxymethylpyrrolidin-1-yl)-5-bromopyridine, 2-(5-hydroxymethylisoxazol)-5-bromopyridine as a starting material, to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.89(s,1H), 8.26(s,3H), 8.12(m,2H), 7.72(t,1H), 7.64 (dd,1H), 7.48(dd,1H), 7.21(s,1H), 5.49(s,2H), 4.77(m,1H), 4.17(t,1H), 3.98 (s,2H), 3.79(m,1H), 3.43(m,2H), 1.83(s,3H)

Example 20: Preparation of (S)-3-(4-(2-(2-oxo-3-glycyloxypyrrolidin-1-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide trifluoroacetic acid (compound 5)

The same procedure as in Example 17 was conducted, except for using, instead of 2-(2-oxo-4-hydroxymethylpyrrolidin-1-yl)-5-bromopyridine, 2-(2-oxo-3-hydroxypyrrolidin-1-yl)-5-bromopyridine as a starting material, to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.60(s,1H), 8.33(d,1H), 8.28(s,3H), 8.25(m,1H), 8.05 (d,1H), 7.63(m,2H), 7.42(dd,1H), 5.78(t,1H), 4.78(m,1H), 4.16(q,2H), 3.98 (s,2H), 3.85(m,1H), 3.78(m,1H), 3.43(m,2H), 2.62(m,1H), 2.12(m,1H), 1.83 (s,3H)

Example 21: Preparation of (S)-3-(4-(2-(5-glycyloxymethyl-[1,2,4]oxadiazol-3-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide trifluoroacetic acid (compound 6)

The same procedure as in Example 17 was conducted, except for using,

instead of 2-(2-oxo-4-hydroxymethylpyrrolidin-1-yl)-5-bromopyridine, 2-(5-hydroxymethyl-[1,2,4]oxadiazol-3-yl)-5-bromopyridine as a starting material, to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.95(s,1H), 8.32(s,3H), 8.21(m,3H), 7.75(t,1H), 7.65 (dd,1H), 7.47(d,1H) 5.67(s,1H), 4.78(m,1H), 4.18(t,1H), 4.05(s,2H), 3.80 (m,1H), 3.43(m,2H), 1.83(s,3H)

Example 22: Preparation of (S)-3-(4-(2-(5-glycyloxymethyl-4,5-dihydroisoxazol-3-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide trifluoroacetic acid (compound 7)

The same procedure as in Example 17 was conducted, except for using, instead of 2-(2-oxo-4-hydroxymethylpyrrolidin-1-yl)-5-bromopyridine, 2-(5-hydroxymethyl-4, 5-dihydroisoxazol-1-yl)-5-bromopyridine as a starting material, to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.81(s,1H), 8.27(t,1H), 8.24(s,3H), 8.05(m,2H), 7.69 (m,2H), 7.44(d,1H) 5.04(m,1H), 4.76(m,1H), 4.41(dd,1H), 4.32(m,1H), 4.17 (t,1H), 3.86(s,2H), 3.77(m,1H), 3.60(m,1H), 3.44(m,2H), 1.83(s,3H)

Example 23: Preparation of (S)-3-(4-(4-(4-glycyloxymethylthiazol-2-yl)phenyl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide trifluoroacetic acid (compound 30)

The same procedure as in Example 17 was conducted, except for using,

instead of 2-(2-oxo-4-hydroxymethylpyrrolidin-1-yl)-5-bromopyridine, 4-(4-hydroxymethyl thiazol-2-yl)-bromobenzene as a starting material, to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.25(s,3H), 8.00(d,2H), 7.85(s,1H), 7.69(m,4H), 7.44 (dd,1H), 5.63(s,2H), 4.76(m,1H), 4.16(t,1H), 3.93(s,2H), 3.79(dd,1H), 3.43 (m,2H), 1.83(s,3H)

Example 24: Preparation of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-([1,2,4]triazol-1-yl)methyl oxazolidin-2-on (compound 4)

1. The Primary Step

In 14ml of methylenchloride was dissolved 1g of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-hydroxymethyl oxazolidin-2-on(compound 10). The solution was added with 0.46g of methansulfonylchloride 0.46g and 0.75ml of triethylamine at room temperature and stirred at the same temperature for 30 minutes. Water and brine were added to the reaction mixture for washing, followed by extraction. The organic layer was dehydrated, filtrated and concentrated in vacuo thereby to provide (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-methansulfonyloxymethyl oxazolidin-2-on 1g. Yield 82%.

2. The Secondary Step

In 15ml of dimethylformamide was dissolved the compound prepared in the primary step. The solution was added with 300mg of 1,2,4-triazol 300㎎ and 100mg of sodiumhydride(60%) at room temperature and stirred for 2 days. The reaction

mixture was extracted with ethyl acetate and then the organic layer, thus separated, was washed with water and brine. The organic layer was dehydrated, filtered and concentrated in vacuo. The residue, prepared by concentrating, was purified by column chromatography to provide the title compound 400mg. Yield 43%.

^{1}H NMR(DMSO-d_6) δ 8.91(s,1H), 8.57(s,1H), 8.19(m,2H), 7.74(t,1H), 7.58 (dd,1H), 7.42(dd,1H), 5.13(m,1H), 4.64(m,2H), 4.46(s,3H), 4.28(t,1H), 3.99 (dd,1H)

Example 25: Preparation of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-([1,2,3]triazol-2-yl)methyl oxazolidin-2-on(compound 8) and (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-([1,2,3]triazol-1-yl)methyl oxazolidin-2-on(compound 9)

The same procedure as in Example 24 was conducted, except for adding, instead of 1,2,4-triazol, 1,2,3-triazol, to obtain compound 8 and compound 9, and then the compounds were divided by column chromatography.

(compound 8) ^{1}H NMR(DMSO-d_6) δ 8.90(s,1H), 8.19(m,2H), 7.82(s,2H), 7.71 (t,1H), 7.59(dd,1H) 7.41(dd,1H), 5.22(m,1H), 4.86(m,2H), 4.46(s,3H), 4.30 (t,1H), 3.98(dd,1H)

(compound 9) ^{1}H NMR(DMSO-d_6) δ 8.90(s,1H), 8.18(m,3H), 7.75(s,1H), 7.72 (t,1H), 7.59(dd,1H) 7.42(dd,1H), 5.22(m,1H), 4.86(m,2H), 4.46(s,3H), 4.30 (t,1H), 3.98(dd,1H)

Example 26: Preparation of (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-([1,2,3]triazol-1-yl)methyl oxazolidin-2-on (compound 13)

The same procedure as in Example 24 was conducted, except for adding 1,2,3-triazo and using the compound 16 as a starting material, to obtain the title compound.

^{1}H NMR(DMSO-d_6) δ 8.92(s,1H), 8.20(s,2H), 8.17(s,1H), 7.75(s,1H), 7.73 (t,1H), 7.61(dd,1H) 7.43(dd,1H), 5.18(m,1H), 4.85(m,2H), 4.29(t,1H), 3.96 (dd,1H), 2.62(s,3H)

Example 27: Preparation of (R)-3-(4-(2-([1,2,4]triazol-1-yl)pyridin-5-yl)-3-fluorophenyl)-5-([1,2,3]triazol-1-yl)methyl oxazolidin-2-on (compound 14)

The same procedure as in Example 24 was conducted, except for adding 1,2,3-triazol and using the compound 17 as a starting material, to obtain the title compound.

^{1}H NMR(DMSO-d_6) δ 9.40(s,1H), 8.70(s,1H), 8.32(s,2H), 8.25(d,1H), 8.17 (s,1H), 7.96(d,1H), 7.75(s,1H), 7.71(t,1H), 7.60(dd,1H) 7.42(dd,1H), 5.18 (m,1H), 4.86(m,2H), 4.29(t,1H), 3.96(dd,1H)

Example 28: Preparation of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-fluoromethyl oxazolidin-2-on (compound 18)

In 5ml of methylenchloride was dissolved 100mg of the compound 10. The

solution was added with 43mg of diethylaminosulfurtrifloride(DAST) and 0.078ml of triethylamine and then stirred for 24 hours. After being concentrating, the reaction mixture was purified by column chromatography to obtain the title compound 75mg. Yield 75%.

^{1}H NMR(DMSO-d_6) δ 8.91(s,1H), 8.19(m,2H), 7.74(t,1H), 7.66(dd,1H) 7.49 (dd,1H), 5.06(m,1H), 4.89(m,2H), 4.46(s,3H), 4.23(t,1H), 3.95(dd,1H)

Example 29: Preparation of (S)-3-(4-(2-(imidazol-1-yl)pyridin-5-yl)-3-fluorophenyl)-5-aminomethyl oxazolidin-2-on hydrochloride (compound 19)

In 3.4ml of ethanol and 30.6ml of pyridin was dissolved 2.5g of (S)-3-(4-(2-(imidazol-1-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide. The solution was added with 2.36g of hydroxylamine at room temperature and stirred for 10 hours at the temperature 100℃. The reaction mixture was extracted with ethyl acetate and the organic layer, thus separated, was washed with water and brine. The organic layer was dehydrated, filtered and concentrated in vacuo. The residue, obtained by concentrating, was purified by column chromatography and then dissolved in tetrahydrofuran solution, saturated hydrochloric acid, and stirred for 10 minutes. The solid, prepared by the above reaction, was recrystalized to provide the title compound 1g.

Example 30: Preparation of (S)-3-(4-(4-(4,5-dimethyloxazol-2-yl)phenyl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide (compound 11)

The same procedure as in Example 1 was conducted, except for adding 4-(4,5-dimethyloxazol-2-yl)-bromobenzene and using (S)-3-(4-trimethylstannyl-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide as a starting material, to obtain the title compound.

^{1}H NMR(DMSO-d_6) δ 8.24(m,1H), 7.96(m,2H), 7.62(m,4H), 7.45(dd,1H), 4.78 (m,1H), 4.16(t,1H), 3.79(dd,1H), 3.41(m,2H), 2.32(s,3H), 2.10(s,3H), 1.83 (s,3H)

Example 31: Preparation of (S)-3-(4-(2-(4,5-dimethyloxazol-2-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide (compound 15)

The same procedure as in Example 1 was conducted, except for adding 4-(4,5-dimethyloxazol-2-yl)-5-bromopyridine and using (S)-3-(4-trimethylstannyl-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide as a starting material, to obtain the title compound.

^{1}H NMR(DMSO-d_6) δ 8.81(s,1H), 8.24(t,1H), 8.07(m,2H), 7.77(t,1H), 7.62 (dd,1H), 7.45(dd,1H), 4.78(m,1H), 4.18(t,1H), 3.79(dd,1H), 3.42(m,2H), 2.35 (s,3H), 2.12(s,3H), 1.84(s,3H)

Example 32: Preparation of (S)-3-(4-(2-([1,2,3]triazol-2-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide (compound 25)

The same procedure as in Example 1 was conducted, except for adding 2-([1,2,3]triazol-2-yl)-5-bromopyridine and using (S)-3-(4-trimethylstannyl-3-

fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide as a starting material, to obtain the title compound.

^{1}H NMR(DMSO-d_6) δ 8.74(s,1H), 8.24(m,2H), 8.19(s,2H), 8.11(d,1H), 7.72 (t,1H), 7.64(dd,1H), 7.45(dd,1H), 4.79(m,1H), 4.18(t,1H), 3.79(dd,1H), 3.43 (m,2H), 1.84(s,3H)

Example 33: Preparation of (S)-3-(4-(4-(4(S)-hydroxymethyl-4,5-dihydrooxazol-2-yl)phenyl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide (compound 26)

The same procedure as in Example 1 was conducted, except for adding 4-(4(S)-hydroxymethyl-4,5-dihydrooxazol-2-yl)-bromobenzene and using (S)-3-(4-trimethylstannyl-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide as a starting material, to obtain the title compound.

^{1}H NMR(DMSO-d_6) δ 8.23(t,1H), 7.91(d,2H), 7.62(m,4H), 7.42(dd,1H), 4.82(t,1H), 4.78(m,1H), 4.41(t,1H), 4.28(m,2H), 4.16(t,1H), 3.79(dd,1H), 3.61 (m,1H), 3.48(m,1H), 3.43(m,2H), 1.84(s,3H)

Example 34: Preparation of (S)-3-(4-(4-(4-cyanomethyl thiazol-2-yl)phenyl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide (compound 31)

The same procedure as in Example 1 was conducted, except for adding 4-(4-cyanomethyl thiazol-2-yl)-bromobenzene and using (S)-3-(4-trimethylstannyl-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide as a starting material, to obtain

the title compound.

^{1}H NMR(DMSO-d_6) δ 8.25(t,1H), 8.00(d,2H), 7.67(m,4H), 7.44(dd,1H), 4.79 (m,1H), 4.23(s,2H), 4.14(t,1H), 3.79(dd,1H), 3.43(m,2H), 1.83(s,3H)

Example 35: Preparation of (R)-3-(4-(4-(4-hydroxymethyl thiazol-2-yl)phenyl)-3-fluorophenyl)-5-([1,2,3]triazol-1-yl)methyl oxazolidin-2-on (compound 36)

The same procedure as in Example 1 was conducted, except for adding 4-(4-hydroxymethyl thiazol-2-yl)-bromobenzene and using (R)-3-(4-trimethylstannyl-3-fluorophenyl)-5-[1,2,3]triazol-1-yl oxazolidin-2-on as a starting material, to obtain the title compound.

^{1}H NMR(DMSO-d_6) δ 8.16(s,1H), 8.00(d,2H), 7.75(s,1H), 7.64(dd,2H), 7.62 (t,1H), 7.52(dd,1H), 7.48(s,1H), 7.36(dd,1H), 5.40(t,1H), 5.18(m,1H), 4.85 (d,2H), 4.62(d,2H), 4.28(t,1H), 3.95(dd,1H)

Example 36: Preparation of (R)-3-(4-(4-(4-glycyloxymethyl thiazol-2-yl)phenyl)-3-fluorophenyl)-5-([1,2,3]triazol-1-yl)methyl oxazolidin-2-on trifluoroacetic acid (compound 37)

The same procedure as in Example 10 was conducted, except for using (R)-3-(4-(4-(4-hydroxymethyl thiazol-2-yl)phenyl)-3-fluorophenyl)-5-[1,2,3]triazol-1-ylmethyl oxazolidin-2-on as a starting material, to obtain the title compound.

^{1}H NMR(DMSO-d_6) δ 8.29(s,3H), 8.17(s,1H), 8.00(d,2H), 7.85(s,1H), 7.75 (s,1H), 7.69(dd,2H), 7.67(t,1H), 7.55(dd,1H), 7.43(dd,1H), 5.36(s,2H), 5.19 (m,1H),

4.86(d,2H), 4.28(t,1H), 4.28(t,1H)

Example 37: Preparation of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-methoxymethyl oxazolidin-2-on (compound 33)

In 10ml of methanol was dissolved 400mg of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-methansulfonyloxymethyl oxazolidin-2-on prepared in the secondary step of the Example 24. The solution was added with 90mg of sodiummethoxide at room temperature and then stirred for one day at room temperature. The solution was extracted with ethyl acetate and the organic layer, thus separated, was washed with water and brine. The organic layer was dehydrated, filtered, concentrated in vacuo and purified by column chromatography to provide the title compound 200mg. Yield 58%.

^{1}H NMR($CDCl_3$) δ 8.90(s,1H), 8.29(d,1H), 8.04(d,1H), 7.61(dd,1H), 7.58 (t,1H), 7.38(dd,1H), 4.80(m,1H), 4.45(s,3H), 4.08(t,1H), 3.96(dd,1H), 3.67 (m,2H), 3.43(s,3H)

Example 38: Preparation of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(N,N-dimethylaminomethyl)oxazolidin-2-on (compound 40)

In 5ml of dimethylformamid was dissolved 100mg of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-methansulfonyloxymethyl oxazolidin-2-on prepared in the secondary step of the Example 24. The solution was added with 30mg of dimethylamine hydrochloride at room temperature. The

solution was stirred for 30 hours at the temperature of 60℃. And then the solution was extracted with ethyl acetate and the organic layer, thus separated, was washed with water and brine. The residue, prepared by dehydrating, filtering and concentrating the organic layer, was purified by column chromatography to provide the title compound 70mg. Yield 76%.

^{1}H NMR(DMSO-d_6) δ 8.91(s,1H), 8.19(m,2H), 7.76(t,1H), 7.65(dd,1H), 7.49(dd,1H), 4.98(m,1H), 4.63(s,3H), 4.27(m,3H), 3.94(dd,1H), 2.79(s,3H), 2.74(s,3H)

Example 39: Preparation of (S)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-N-methylaminomethyl oxazolidin-2-on (compound 41)

In 7ml of dimethylformamid was dissolved 200mg of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-methansulfonyloxymethyl oxazolidin-2-on, prepared in the primary step of the Example 24. The solution was added with 100mg of methylamine hydrochloride and 240mg of potasiumcarbonate at room temperature. The solution was stirred for 30 hours at the temperature of 80℃. The solution was added with ethyl acetate and then the organic layer, thus separated, was washed with water and brine. The residue, prepared by dehydrating, filtering and concentrating the organic layer, was purified by column chromatography to obtain the title compound 80mg. Yield 45%.

^{1}H NMR(DMSO-d_6) δ 8.91(s,1H), 8.18(m,2H), 7.73(t,1H), 7.66(dd,1H), 7.47 (dd,1H), 7.17(m,1H), 4.94(m,1H), 4.46(s,3H), 4.25(m,3H), 3.85(dd,1H), 2.49

(d,3H)

Example 40: Preparation of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-alanyloxy)methyl oxazolidin-2-on trifluoroacetic acid (compound 42)

The same procedure as in Example 10 was carried out to provide the title compound using BOC-L-alanine instead of BOC-glycine.

^{1}H NMR(DMSO-d_6) δ 8.91(s,1H), 8.42(s,3H), 8.20(m,2H), 7.75(t,1H), 7.67 (dd,1H), 7.48(dd,1H), 5.05(m,1H), 4.61(dd,1H), 4.46(s,3H), 4.41(dd,1H), 4.26 (t,1H), 4.18(m,1H), 3.96(dd,1H), 1.36(d,3H)

Example 41: Preparation of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-valyloxy)methyl oxazolidin-2-on hydrochloride (compound 43)

500mg of compound 20, prepared in Example 11, was dissolved in water. The solution was controlled to pH 5 with the addition of sodium bicarbonate aqueous solution. The aqueous layer was extracted with ethyl acetate and then the organic layer was slowly added with ether solution saturating of hydrochloric acid. The solid prepared by the above method was filtered and concentrated in vacuo to provide the title compound 200mg. Yield 46%.

^{1}H NMR(DMSO-d_6) δ 8.92(s,1H), 8.54(bs,3H), 8.20(m,2H), 7.76(t,1H), 7.65 (dd,1H), 7.49(dd,1H), 5.04(m,1H), 4.58(dd,1H), 4.46(s,3H), 4.41(dd,1H), 4.26

(t,1H), 3.95(m,2H), 2.17(m,1H), 0.97(d,3H), 0.94(d,3H)

Example 42: Preparation of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-alanyloxy)methyl oxazolidin-2-on hydrochloride (compound 44)

With the exception of using compound 42, the same procedure as in Example 41 was conducted to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.92(s,1H), 8.52(bs,3H), 8.20(m,2H), 7.75(t,1H), 7.66 (dd,1H), 7.49(dd,1H), 5.05(m,1H), 4.60(dd,1H), 4.46(s,3H), 4.41(dd,1H), 4.26 (t,1H), 4.18(m,1H), 4.00(dd,1H), 1.37(d,3H)

Example 43: Preparation of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on hydrochloride (compound 45)

With the exception of using the compound 12, the same procedure as in Example 41 was conducted to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.91(s,1H), 8.48(bs,3H), 8.18(m,2H), 7.75(t,1H), 7.65(dd,1H), 7.49(dd,1H), 5.03(m,1H), 4.48(m,2H), 4.46(s,3H), 4.24(t,1H), 3.99(dd,1H), 3.86(m,2H)

Example 44 : Preparation of (S)-3-(4-(4-(4-hydroxymethylthiazol-2-yl)phenyl)-3-fluorophenyl)-2-oxo-5-oxazolidinylmethyl acetamide (compound 28)

With the exception of using (S)-3-(4-trimethylstannyl-3-fluorophenyl)-2-

oxo-5-oxazolidinylmethyl acetamide as a starting material and 4-(4-hydroxymethylthiazol-2-yl)-bromobenzene, the same procedure as in Example 1 was conducted to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.24(t,1H), 7.98(d,2H), 7.65(m,2H), 7.59(m,2H), 7.43 (s,1H), 7.41(dd,1H), 5.40(t,1H), 4.79(m,1H), 4.63(d,2H), 4.16(t,1H), 3.79 (dd,1H), 3.43(m,2H), 1.84(s,3H)

Example 45: (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L- prolinyloxy)methyl oxazolidin-2-on trifluoroacetic acid (compound 46)

With the exception of using BOC-L-proline, instead of BOC-glycine, the same procedure as in Example 10 was conducted to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 9.25(bs,2H), 8.91(s,1H), 8.20(m,2H), 7.76(t,1H), 7.65(dd,1H), 7.48(dd,1H), 5.05(m,1H), 4.57(dd,1H), 4.45(s,3H), 4.41(dd,1H), 4.26(t,1H), 3.96(dd,1H), 3.23(m,2H), 2.21(m,1H), 1.92(m,3H)

Example 46: Preparation of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L- prolinyloxy)methyl oxazolidin-2-on hydrochloride (compound 47)

With the exception of using the compound 46, the same procedure as in Example 41 was conducted to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 9.11(bs,2H), 8.91(s,1H), 8.20(m,2H), 7.76(t,1H), 7.65(dd,1H), 7.49(dd,1H), 5.05(m,1H), 4.55(dd,1H), 4.46(s,3H), 4.41(dd,1H),

4.25(t,1H), 4.01(dd,1H), 3.36(m,2H), 2.07(m,1H), 1.89(m,3H)

Example 47: Preparation of (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on hydrochloride (compound 48)

With the exception of using the compound 27, the same procedure as in Example 41 was conducted to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.92(s,1H), 8.48(s,3H), 8.21(s,2H), 7.76(t,1H), 7.66 (dd,1H), 7.48(dd,1H), 5.04(m,1H), 4.47(m,2H), 4.23(t,1H), 3.94(m,1H), 3.84 (d,2H), 2.62(s,3H)

Example 48: Preparation of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(β-alanyloxy)methyl oxazolidin-2-on trifluoroacetic acid (compound 49)

With the exception of using BOC-β-alanine, instead of BOC-glycine, the same procedure as in Example 10 was conducted to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.91(s,1H), 8.20(m,2H), 7.75(t,1H), 7.73(bs,3H), 7.68(dd,1H), 7.48(dd,1H), 5.02(m,1H), 4.46(s,3H), 4.36(m,2H), 4.26(t,1H), 3.93(dd,1H), 3.02(m,2H), 2.70(t,2H)

Example 49: Preparation of (R)-3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(β-alanyloxy)methyl oxazolidin-2-on hydrochloride (compound

50)

With the exception of using the compound 49, the same procedure as in Example 41 was conducted to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.91(s,1H), 8.22(m,2H), 8.11(bs,3H), 7.76(t,1H), 7.65 (dd,1H), 7.48(dd,1H), 5.02(m,1H), 4.46(s,3H), 4.36(m,2H), 4.23(t,1H), 3.95 (m,1H), 3.00(m,2H), 2.74(t,2H)

Example 50: Preparation of (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-alanyloxy)methyl oxazolidin-2-on trifluoroacetic acid(compound 51)

With the exception of using the compound 16 and BOC-L-alanine, the same procedure as in Example 10 was conducted to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.93(s,1H), 8.39(bs,3H), 8.21(s,2H), 7.76(t,1H), 7.68 (dd,1H), 7.49(dd,1H), 5.04(m,1H), 4.61(dd,1H), 4.40(dd,1H), 4.28(t,1H), 4.18 (dd,1H), 3.95(dd,1H), 2.62(s,3H), 1.36(d,3H)

Example 51: Preparation of (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-alanyloxy)methyl oxazolidin-2-on hydrochloride (compound 52)

With the exception of using the compound 51, the same procedure as in Example 41 was conducted to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.93(s,1H), 8.61(bs,3H), 8.21(s,2H), 7.76(t,1H),

7.65(dd,1H), 7.49(dd,1H), 5.05(m,1H), 4.58(dd,1H), 4.39(dd,1H), 4.25(t,1H), 4.12(m,1H), 4.00(dd,1H), 2.62(s,3H), 1.36(d,3H)

Example 52: Preparation of (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-valyloxy)methyl oxazolidin-2-on trifluoroacetic acid (compound 53)

With the exception of using the compound 16 and BOC-L-valline, the same procedure as in Example 10 was conducted to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.93(s,1H), 8.40(bs,3H), 8.21(s,2H), 7.75(t,1H), 7.68(dd,1H), 7.48(dd,1H), 5.04(m,1H), 4.62(dd,1H), 4.40(dd,1H), 4.26(t,1H), 3.99(d,1H), 3.92(dd,1H), 2.62(s,3H), 2.12(m,1H), 0.97(d,3H), 0.94(d,3H)

Example 53: Preparation of (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-valyloxy)methyl oxazolidin-2-on hydrochloride (compound 54)

With the exception of using the compound 53, the same procedure as in Example 41 was conducted to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.93(s,1H), 8.60(bs,3H), 8.21(s,2H), 7.75(t,1H), 7.67(dd,1H), 7.49(dd,1H), 5.04(m,1H), 4.58(dd,1H), 4.42(dd,1H), 4.26(t,1H), 3.92(m,1H), 2.62(s,3H), 2.12(m,1H), 0.97(d,3H), 0.94(d,3H)

Example 54: Preparation of (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-

5-yl)-3-fluorophenyl)-5-(L-prolinyloxy)methyl oxazolidin-2-on trifluoroacetic acid (compound 55)

With the exception of using the compound 16 and BOC-L-prroline, the same procedure as in Example 10 was conducted to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 9.20(bs,2H), 8.93(s,1H), 8.21(s,2H), 7.77(t,1H), 7.66(dd,1H), 7.50(dd,1H), 5.04(m,1H), 4.59(dd,1H), 4.43(m,2H), 4.26(t,1H), 3.96(dd,1H), 3.21(m,2H), 2.62(s,3H), 2.21(m,1H), 1.95(m,1H), 1.89(m,2H)

Example 55: Preparation of (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-prolinyloxy)methyl oxazolidin-2-on hydrochloride (compound 56)

With the exception of using the compound 55, the same procedure as in Example 41 was conducted to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 9.18(bs,2H), 8.93(s,1H), 8.21(s,2H), 7.76(t,1H), 7.65(dd,1H), 7.49(dd,1H), 5.05(m,1H), 4.57(dd,1H), 4.43(m,2H), 4.26(t,1H), 4.00(dd,1H), 3.21(m,2H), 2.62(s,3H), 2.21(m,1H), 1.95(m,1H), 1.89(m,2H)

Example 56: Preparation of (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(β-alanyloxy)methyl oxazolidin-2-on trifluoroacetic acid (compound 57)

With the exception of using the compound 16 and BOC-β-allanine, the same procedure as in Example 10 was conducted to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.92(s,1H), 8.21(s,2H), 7.88(bs,3H), 7.76(t,1H), 7.68(dd,1H), 7.49(dd,1H), 5.02(m,1H), 4.36(m,2H), 4.25(t,1H), 3.94(dd,1H), 3.03(m,2H), 2.70(t,2H), 2.62(s,3H)

Example 57: Preparation of (R)-3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(β-alanyloxy)methyl oxazolidin-2-on hydrochloride (compound 58)

With the exception of using the compound 57, the same procedure as in Example 41 was conducted to prepare the title compound.

^{1}H NMR(DMSO-d_6) δ 8.92(s,1H), 8.21(s,2H), 8.08(bs,3H), 7.76(t,1H), 7.68(dd,1H), 7.49(dd,1H), 5.02(m,1H), 4.36(m,2H), 4.25(t,1H), 3.96(dd,1H), 3.00(m,2H), 2.71(t,2H), 2.62(s,3H)

Example 58: Preparation of mono-[(R)-[3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl] phosphate(compound 72) and (R)-[3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl disodiumphosphate (compound 59)

1. The Primary Step

In 10ml of mixture solvent(tetrahydrofuran : methylenchloride = 1:1) was dissolved 1g of compound 10. The solution was added with 0.6g of tetrazole and 2.3g of di-tetrabuthyl diisoprophylphosphoamidite and stirred for 15 hours at room temperature. The reaction mixture was refrigerated to −78℃, added with 0.7g of

metachloroperbenzoic acid and stirred for 2 hours. After being cooling to –78℃, the reaction mixture was added with metachloroperbenzoic acid (0.7g). When the reaction mixture was stirred for 2 hours, the temperature of the reaction mixture was raised to room temperature. The reaction mixture was then added with ethyl acetate. The organic layer, thus separated, was washed with sodiumbisulfate, sodiumbicarbonate and brine, dehydrated, filtered and concentrated in vacuo, followed by purification with column chromatography thereby to provide (R)-[3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl phosphoric acid ditetrabuthylester (0.71g, 71%).

^{1}H NMR(DMSO-d_6) δ 8.90(s,1H), 8.18(m,2H), 7.74(t,1H), 7.68 (dd,1H), 7.49(dd,1H), 4.98(m,1H), 4.46(s,3H), 4.23(t,1H), 4.18(m,1H), 4.09(m,1H), 3.89 (dd,1H), 1.39(s,9H), 1.38(s,9H)

The crystal prepared the above method was dissolved in a mixture of methanol and chloroform. And then the solution added with 3.4ml of sodiummethoxide(0.3M methanol solution) at the room temperature and stirred for 10 hours. The reaction mixture was concentrated to prepare the residue. The residue was crystallized and filtered thereby to obtain the title compound(compound 59) 300mg.

^{1}H NMR(D_2O) δ 8.27(s,1H), 7.56(dd,2H), 7.06(m,2H), 6.90(m,1H), 4.79 (m,1H), 4.63(s,3H), 3.90(m,4H)

2. The Secondary Step

In 30ml of methylenchloride was dissolved the compound(0.7g) in the Primary Step. The solution was added with 15ml of trifluoroacetic acid and then stirred for 1 hour at room temperature. The reaction mixture was concentrated in vacuo to prepare the residue. The residue was crystallized with ethanol and ethyl ether to obtain mono-[(R)-[3-(4-(2-(2-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl] phosphate (compound 72) 400mg.

^{1}H NMR(DMSO-d_6) δ 8.92(s,1H), 8.20(m,2H), 7.74(t,1H), 7.66(dd,1H), 7.500(dd,1H), 4.95 (m,1H), 4.46(s,3H), 4.21(t,1H), 4.05(m,2H), 3.91(dd,1H)

Example 59: Preparation of (R)-[3-(4-(2-(2-methyl-[1,3,4]oxadiazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl disodiumphosphate (compound 60)

Using the compound 16, the title compound was prepared in a manner similar to that of the Example 58.

^{1}H NMR(D_2O) δ 8.33(s,1H), 7.65(dd,2H), 7.17(m,2H), 6.90(m,1H), 4.79 (m,1H), 4.63(s,3H), 3.94(t,1H), 3.78(m,3H)

Example 60: Preparation of (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-hydroxymethyl oxazolidin-2-on (compound 61)

Using 2-(1-methyltetrazol-5-yl)-5-bromopyridine, the title compound was prepared in a manner similar to that of the Example 1.

^{1}H NMR(DMSO-d_6) δ 8.98(s,1H), 8.30(m,2H), 7.75(m,2H), 7.53(dd,1H), 5.25(t,1H), 4.76(m,1H), 4.44(s,3H), 4.14(t,1H), 3.89(dd,1H), 3.69(m,1H), 3.58 (m,1H)

Example 61: Preparation of (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on trifluoroacetic acid (compound 62)

Using 2-(1-methyltetrazol-5-yl)-5-bromopyridine, the title compound was prepared in a manner similar to that of the Example 10.

^{1}H NMR(DMSO-d_6) δ 8.95(s,1H), 8.20(s,3H), 8.19(m,2H), 7.80(t,1H), 7.69 (dd,1H), 7.49(dd,1H), 5.00(m,1H), 4.46(m,2H), 4.45(s,3H), 4.24(t,1H), 3.92 (dd,1H), 3.90(s,2H)

Example 62: Preparation of (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-glycyloxymethyl oxazolidin-2-on hydrochloride (compound 63)

Using 2-(1-methyltetrazol-5-yl)-5-bromopyridine, the title compound was prepared in a manner similar to that of the Example 43.

^{1}H NMR(DMSO-d_6) δ 8.95(s,1H), 8.50(bs,3H), 8.21(m,2H), 7.80(t,1H), 7.65(dd,1H), 7.49(dd,1H), 5.03(m,1H), 4.48(m,2H), 4.43(s,3H), 4.24(t,1H), 3.99(dd,1H), 3.86(m,2H)

Example 63: Preparation of (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-

fluorophenyl)-5-(L-alanyloxy)methyl oxazolidin-2-on trifluoroacetic acid (compound 64)

Using 2-(1-methyltetrazol-5-yl)-5-bromopyridine, the title compound was prepared in a manner similar to that of the Example 40.

^{1}H NMR(DMSO-d_6) δ 8.95(s,1H), 8.43(s,3H), 8.25(m,2H), 7.77(t,1H), 7.68 (dd,1H), 7.48(dd,1H), 5.05(m,1H), 4.63(dd,1H), 4.44(s,3H), 4.42(dd,1H), 4.24 (t,1H), 4.18(m,1H), 3.98(dd,1H), 1.36(d,3H)

Example 64: Preparation of (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-alanyloxy)methyl oxazolidin-2-on hydrochloride (compound 65)

Using 2-(1-methyltetrazol-5-yl)-5-bromopyridine, the title compound was prepared in a manner similar to that of the Example 42.

^{1}H NMR(DMSO-d_6) δ 8.95(s,1H), 8.53(bs,3H), 8.24(m,2H), 7.77(t,1H), 7.67(dd,1H), 7.49(dd,1H), 5.05(m,1H), 4.60(dd,1H), 4.43(s,3H), 4.42(dd,1H), 4.26(t,1H), 4.20(m,1H), 4.00(dd,1H), 1.37(d,3H)

Example 65: Preparation of (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-valyloxy)methyl oxazolidin-2-on trifluoroacetic acid (compound 66)

Using 2-(1-methyltetrazol-5-yl)-5-bromopyridine, the title compound was prepared in a manner similar to that of the Example 11.

^{1}H NMR(DMSO-d_6) δ 8.95(s,1H), 8.42(s,3H), 8.25(m,2H), 7.79(t,1H), 7.70 (dd,1H), 7.48(dd,1H), 5.05(m,1H), 4.64(dd,1H), 4.44(s,3H), 4.43(dd,1H), 4.30 (t,1H), 4.01(d,1H), 3.93(dd,1H), 2.14(m,1H), 0.98(d,3H), 0.95(d,3H)

Example 66: Preparation of (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(L-valyloxy)methyl oxazolidin-2-on hydrochloride (compound 67)

Using 2-(1-methyltetrazol-5-yl)-5-bromopyridine, the title compound was prepared in a manner similar to that of the Example 41.

^{1}H NMR(DMSO-d_6) δ 8.94(s,1H), 8.57(bs,3H), 8.22(m,2H), 7.79(t,1H), 7.67(dd,1H), 7.49(dd,1H), 5.04(m,1H), 4.59(dd,1H), 4.43(s,3H), 4.41(dd,1H), 4.27(t,1H), 3.99(m,2H), 2.17(m,1H), 0.97(d,3H), 0.94(d,3H)

Example 67: Preparation of (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(β-alanyloxy)methyl oxazolidin-2-on trifluoroacetic acid (compound 68)

Using 2-(1-methyltetrazol-5-yl)-5-bromopyridine, the title compound was prepared in a manner similar to that of the Example 48.

^{1}H NMR(DMSO-d_6) δ 8.94(s,1H), 8.24(m,2H), 7.77(t,1H), 7.73(bs,3H), 7.70(dd,1H), 7.49(dd,1H), 5.02(m,1H), 4.44(s,3H), 4.36(m,2H), 4.27(t,1H), 3.93(dd,1H), 3.05(m,2H), 2.70(t,2H)

Example 68: Preparation of (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(β-alanyloxy)methyl oxazolidin-2-on hydrochloride (compound 69)

Using 2-(1-methyltetrazol-5-yl)-5-bromopyridine, the title compound was prepared in a manner similar to that of the Example 49.

^{1}H NMR(DMSO-d_6) δ 8.96(s,1H), 8.25(m,2H), 8.13(bs,3H), 7.79(t,1H), 7.66(dd,1H), 7.48(dd,1H), 5.02(m,1H), 4.43(s,3H), 4.36(m,2H), 4.25(t,1H), 3.97(m,1H), 3.01(m,2H), 2.74(t,2H)

Example 69: Preparation of mono-[(R)-[3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl] phosphate(compound 73) and (R)-[3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl disodiumphosphate(compound 70)

1. The Primary Step

Using the compound 61, (R)-[3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl phosphoric acid ditetrabuthylester was prepared in a manner similar to that of the Example 58.

^{1}H NMR(DMSO-d_6) δ 8.94(s,1H), 8.20(m,2H), 7.78(t,1H), 7.68 (dd,1H), 7.49(dd,1H), 4.98(m,1H), 4.44(s,3H), 4.21(t,1H), 4.18(m,1H), 4.10(m,1H), 3.89 (dd,1H), 1.39(s,9H), 1.38(s,9H)

2. The Secondary Step

Using the compound provided in the Primary Step, 400mg of mono-[(R)-[3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl] phosphate (compound 73) was prepared in a manner similar to that of the Example 58

^{1}H NMR(DMSO-d_6) δ 8.95(s,1H), 8.23(m,2H), 7.76(t,1H), 7.66(dd,1H), 7.500(dd,1H), 4.95 (m,1H), 4.44(s,3H), 4.21(t,1H), 4.05(m,2H), 3.91(dd,1H)

The title compound(compound 70) was obtained in a manner similar to that of the Example 58.

^{1}H NMR(D_2O) δ 8.29(s,1H), 7.60(dd,2H), 7.10(m,2H), 6.90(m,1H), 4.79 (m,1H), 4.60(s,3H), 3.90(m,4H)

Example 70: Preparation of (R)-3-(4-(2-(1-methyltetrazol-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-([1,2,3]triazol-1-yl)methyl oxazolidin-2-on(compound 71)

Using the compound 61, the title compound was prepared in a manner similar to that of the Example 24.

^{1}H NMR(DMSO-d_6) δ 8.95(s,1H), 8.21(m,3H), 7.77(s,1H), 7.75 (t,1H), 7.59(dd,1H) 7.42(dd,1H), 5.22(m,1H), 4.86(m,2H), 4.44(s,3H), 4.31 (t,1H), 3.98(dd,1H)

Experimental Example 1: Assay for in vitro Antibacterial Activity.

To test an antibacterial activity of the derivatives of oxazolidinone, the

antibacterial activity, including methicillin resistant *Staphylococcus aureus*(MRSA) and vancomycin resistant *Enterococci*(VRE), was represented as Minimum Inhibitory Concentration(MIC_{50}, μg/mℓ) using agar dilution described in a art(*Chemotheraphy*, 29(1), 76, (1981)). Zyvox of Pharmacia & Upjohn Inc, corresponding to Formula 3, was used as control. The results are shown in Table 2.

[Table 2]

Compound	Minimum Inhibitory Concentration (MIC_{50}, μg/mℓ)		Compound	Minimum Inhibitory Concentration (MIC_{50}, μg/mℓ)	
	MRSA	VRE		MRSA	VRE
Zyvox	2	2	37	0.5	0.5
1	1	0.25	38	0.5	1
2	0.5	0.125	39	1	1
3	0.25	0.25	40	4	8
4	2	2	41	4	8
5	0.5	0.25	42	0.5	0.25
6	NA	NA	43	0.5	0.25
7	0.5	0.5	44	0.5	0.25
8	16	16	45	0.5	0.25
9	0.25	0.125	46	0.5	0.25
10	0.5	0.25	47	0.5	0.25
11	0.5	0.25	48	0.5	1

12	0.5	0.25	49	0.5	0.25
13	0.25	0.25	50	0.5	0.25
14	0.25	0.25	51	0.5	1
15	1	1	52	0.5	1
16	0.5	1	53	0.5	1
17	1	1	54	0.5	1
18	1	2	55	0.5	1
19	32	32	56	0.5	1
20	0.5	0.25	57	0.5	1
21	1	1	58	0.5	1
22	1	1	59	0.5	0.25
23	2	2	60	0.5	1
24	0.5	0.5	61	0.5	0.25
25	0.25	0.125	62	0.5	0.25
26	0.5	0.5	63	0.5	0.25
27	0.5	1	64	0.5	0.25
28	0.5	0.5	65	0.5	0.25
29	0.5	1	66	0.5	0.25
30	0.5	0.5	67	0.5	0.25
31	0.5	0.5	68	0.5	0.25
32	0.5	1	69	0.5	0.25

33	2	2	70	0.5	0.25
34	1	1	71	0.5	0.125
35	1	1	72	32	32
36	0.5	0.5	73	32	32

NA : Not determined

MRSA : methicillin resistant *Staphylococcus aureus*

VRE : vancomycin resistant *Enterococci*

As illustrated in Table 2, the derivatives of the present invention had sufficient efficiency on antibacterial activity against *Staphylococcus aureus*(MRSA) and *Enterococci*(VRE) in spite of using lower concentration of the derivatives than that of the Zyvox. Accordingly, the compounds of the present invention may be useful as antibiotics.

Experimental Example 2: Assay for solubility

To test a solubility of the derivatives of the present invention, an experiment was carried out below. The derivatives of the present invention were added to 200㎕ of distilled water and then the solution was stirred for 2 minutes. The turbidity of the solution was watched through naked eye.

When the derivatives were not dissolved completely, 50㎕ of distilled water was added to the solution and then the turbidity of the solution was assayed in the above manner to find a point of becoming transparent solution.

When 2mg of the derivatives was first added to distilled water and completely dissolved so that the solution became transparent, 2mg of the derivatives was added more to the solution and then state of the solution was watched. The derivatives of the present invention were added to the five times and then solubility of the solution was assayed for. The assay for solubility was carried out the three times repeatedly in the above method and the results were averaged. The averages were shown in Table 3.

[Table 3]

Compound	Solubility	Compound	Solubility
Zyvox	3 mg/mℓ	51	>50 mg/mℓ
10	10 μg/mℓ	52	>50 mg/mℓ
12	28 mg/mℓ	53	30.3 mg/mℓ
16	20 μg/mℓ	54	2.9 mg/mℓ
20	4.7 mg/mℓ	55	7.2 mg/mℓ
27	>50 mg/mℓ	56	>50 mg/mℓ
42	>50 mg/mℓ	57	>50 mg/mℓ
43	4.2 mg/mℓ	58	5.5 mg/mℓ
44	>50 mg/mℓ	59	>50 mg/mℓ
45	12 mg/mℓ	60	>50 mg/mℓ
46	<1.63 mg/mℓ	62	28 mg/mℓ
47	2 mg/mℓ	64	>50 mg/mℓ
48	>50 mg/mℓ	66	4.7 mg/mℓ

49	2.6 mg/mℓ	68	2.6 mg/mℓ
50	20.4 mg/mℓ	70	>50 mg/mℓ

As shown in table 3, the solubility of the compound 42(>50 mg/mℓ) that is prodruged, of the derivatives was enhanced as compared with those of Zyvox(3 mg/mℓ) and the compound 10(10 ㎍/mℓ).

Accordingly, when the derivatives of the present invention were formulated for oral administration, absorption of the derivatives may be enhanced. When the derivatives were formulated as injection, various formations of the derivatives may be obtained.

Experimental Example 3: Test of acute toxicity by oral administrating the derivatives to mouse

To test acute toxicity of the compounds of the present invention, the following experiment was carried out.

A mixture of 1% hydroxyprophylmethylcellulose and 200mg of one selected from the group consisting of the compounds 10, 12, 16, 17, 20, 22, 24 and 27 was administrated to 5 ICR mice(5-Week old males, 20g ± 2g by weight). And then lethality for 2 weeks, weight, symptoms etc. was watched to determine Minimum Lethal Dose(MLD, mg/kg). Zyvox of Pharmacia & Upjohn Inc was used as control. The results were represented in Table 4.

[Table 4]

Compound	Minimum Lethal Dose (MLD, mg/kg)
Zyvox	>1000
10	>1000
12	>1000
16	>1000
17	>1000
20	>1000
22	>1000
24	>1000
27	>1000

Observation of survival, change in weight, tests in blood, and toxicity syndrome, etc. proved that administration of the composition of the present invention has no toxic effects

The compounds of the present invention have excellent efficiency on antibacterial activity without any toxicity present according to Table 4.

Example Formulation: Preparation of Pharmaceutical composition

1. Preparation as powder

Derivative of oxazolidinone	2g
Lactose	1g

The above materials were mixed and then the mixture was filled into a closed pack to prepare as powder.

2. Preparation as tablet

Derivative of oxazolidinone	500mg
Corn starch	100mg
Lactose	100mg
Magneisuim stearate	2mg

The above materials were mixed and then the mixture was tabletted by the known method to prepare as tablet.

3. Preparation of capsule

Derivative of oxazolidinone	500mg
Corn starch	100mg
Lactose	100mg
Magneisuim stearate	2mg

The above materials were mixed and the mixture was filled into gelatin capsule by the known method to prepare as capsule.

4. Preparation of injection

Derivative of oxazolidinone	500mg
Citrate buffer	maintaining of pH 3.5

Dextrose isotonicity

The derivative of oxazolidine, salt of sodium citrate, citratic acid and dextrose were filled in 20㎖ of vial, sterilized, for injection and then sealed off using aluminum cap. The mixture was dissolved in distilled water for injection and then diluted in distilled water solution, having appropriate volume, for injection.